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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,794	03/17/2005	Jorge Victor Gavilondo Cowley	976-20PCT/US	6673
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HOFFMANN & BARON, LLP			BRISTOL, LYNN ANNE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/511,794	GAVILONDO COWLEY ET AL.
	Examiner Lynn Bristol	Art Unit 1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 05 October 2007.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 32-46 is/are pending in the application.
- 4a) Of the above claim(s) 37,38,44 and 45 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 32-36, 39-43 and 46 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____.

 | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

1. Claims 32-46 are all the pending claims for this application.

2. Claims 1-31 were canceled and new claims 32-46 were added in the response of 10/5/07.

3. Applicants original election without traverse of claims for examination in the Reply of 3/29/07 was drawn to antibodies and pharmaceutical compositions. New claims 32-36, 39-42 and 46 read on the originally elected claims and examined by original presentation. This application now contains Claims 37, 38, 44 and 45 drawn to method invention(s) that were not originally presented. Further, Claims 37 and 44 are drawn to methods for identifying human CEA-expressing tumor cells using the monomeric or dimeric antibody and method Claims 38 and 45 are drawn methods for treating human CEA-expressing tumor cells using the monomeric or dimeric antibody. The method claims are separate and distinct from the other because they require different steps, have different intended populations, and have different intended outcomes (See MPEP § 806.05(j)). Further, the examined and new claims for the CEA antibodies and pharmaceutical compositions are separate and distinct from the new method claims because each of the inventive methods could be practiced with a materially different reagent (See MPEP § 806.05(h)).

Thus Claims 37, 38, 44 and 45 are withdrawn from examination. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 32-36, 39-42 and 46 are all the pending claims under examination.

5. Applicants amendment of the claims raises new grounds for rejection. **This action is FINAL.**

Withdrawal of Objections

Specification

6. The objection to the specification for failing to include sequence identifiers for the sequences: a) (²⁰Phe-Arg³¹)-S-S-(⁸⁷Ser-Arg⁹⁷) (p. 20, lines 19-20); and b) (¹⁴³Val-Lys¹⁴⁸)-S-S-(¹⁸⁶11e-Lys²²⁸) (p. 20, line 20) pursuant to 37 CFR 1.821 (c) and/or (d) is withdrawn.

Applicants' amendment of the specification on p. 2 of the Response of 10/5/07 to correct the figure legend of Figure 4 to include SEQ ID NOS: obviates the objection.

Applicants' comments on p. 13 of the Response of 10/5/07 are acknowledged.

7. The objection to the specification for the improper use of trademarks, e.g., TriPure™, Lipofectamine PLUS™ is withdrawn.

Applicants' amendment of the specification on pp. 2-3 of the Response of 10/5/07 obviates the objection.

Applicants' comments on p. 13 of the Response of 10/5/07 are acknowledged.

8. The objection to the specification for the misspelled terms "aminoacid" and "aminoacidic" to recite "amino acid" obviated the objection.

Applicants' comments on p. 13 of the Response of 10/5/07 are acknowledged.

Claim Objections

9. The objection to Claims 2, 4 and 6 for misspelling the term "aminoacid" is withdrawn and obviated in view of the cancelled claims.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

10. The rejection of Claims 1, 2, 5 and 7-11 for the recitation "of the monomeric scFv type obtained from the RNA extracted from the hybridoma producing Mab CB/ior-CEA.1" in Claim 1 is withdrawn and moot in view of the cancelled claims.

11. The rejection of Claims 3, 4, 15, 16, 18, 20, 22 and 24 are indefinite for the recitation "of the divalent (diabody) scFv type obtained from the RNA extracted from the hybridoma producing Mab CB/ior-CEA.1" in Claim 3 is withdrawn and moot in view of the cancelled claims.

12. The rejection of Claims 1-5, 7-11, 15, 16, 18, 20, 22 and 24 in lacking antecedent basis for the limitation "such antigen" in Claims 1 and 3 is withdrawn and moot in view of the cancelled claims.

13. The rejection of Claims 1-5, 7-11, 15, 16, 18, 20, 22 and 24 for the recitation "dependent on the conservation of *its* glycosylation" in Claims 1 and 3 is withdrawn and moot in view of the cancelled claims.
14. The rejection of Claims 6, 17, 19, 21, 23 and 25 for the recitation "or fused to biologically or biochemically active domains" in Claim 6 is withdrawn and moot in view of the cancelled claims.
15. The rejection of Claims 6, 17, 19, 21, 23 and 25 for the recitation "other scFv variants" in Claim 6 is withdrawn and moot in view of the cancelled claims.
16. The rejection of Claims 7, 16 and 17 for the recitation "in insect or mammalian transfected cells" is withdrawn and moot in view of the cancelled claims.
17. The rejection of Claims 8, 18 and 19 for the recitation "or detectable by other method" is withdrawn and moot in view of the cancelled claims.
18. The rejection of Claims 11, 24 and 25 for the recitation "linked or not to cells" is withdrawn and moot in view of the cancelled claims.

Claim Rejections - 35 USC § 112, first paragraph

Biological Deposit Requirement

19. The rejection of Claims 1, 3, 5, 7-11, 15, 16, 18, 20, 22 and 24 in lacking enablement for the hybridoma cell lines is withdrawn and moot in view of the cancelled claims.

Scope of Enablement

20. The rejection of Claims 9, 20 and 21 under 35 U.S.C. 112, first paragraph, because the specification, in lacking enablement for using the antibody of SEQ ID NO: 16 or 17 in a pharmaceutical composition to treat any human with any CEA-expressing tumor is withdrawn and moot in view of the cancelled claims.

Claim Rejections - 35 USC § 103

21. The rejection of Claims 1, 3, 5-8, 10, 11, 15-19, and 22-25 under 35 U.S.C. 103(a) as being unpatentable over Tormo et al. (APMIS 97(12):1073-80 (1989); cited in the 892 form of 3/6/07' Abstract) in view of Freyre et al. (J. Biotechnol. 76:157-163 (2000)) as evidenced by Ayala et al. (Conf. On Plant-Made Pharmaceuticals 2005; Abstract) and further in view of Hollinger et al. (PNAS 90:6444-6448 (1993); cited in the IDS of 1/24/05 and the 892 form of 3/6/07) is withdrawn and moot in view of the cancelled claims.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
- a) Claim 46 is indefinite for the recitation "comprising an amino acid sequence as set forth in SEQ ID NO:16 and SEQ ID NO:17" because it is not clear if the antibody should comprise both the monomeric (SEQ ID NO:16) and dimeric (SEQ ID NO:17) sequences within the same molecule to produce a trivalent antibody, or whether the antibody comprises one or the other scFv. The specification teaches the production of the monovalent scFv and the divalent scFv or diabody (Example 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

23. Claims 32-36, 39-42 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tormo et al. (APMIS 97(12):1073-80 (1989); cited in the 892 form of 3/6/07; Abstract) in view of Freyre et al. (J. Biotechnol. 76:157-163 (2000); cited in the PTO 892 form of 6/7/07) as evidenced by Ayala et al. (Conf. On Plant-Made Pharmaceuticals 2005; Abstract; cited in the PTO 892 form of 6/7/07) and further in view of Hollinger et al. (PNAS 90:6444-6448 (1993); cited in the IDS of 1/24/05 and the 892 form of 3/6/07).

Claims 32-36 are interpreted as being drawn to a monomeric scFV comprising amino acid sequence of SEQ ID NO:16 which binds to human CEA (Claim 32), further comprising a detectable agent (Claim 33), further where the detectable agent is a radioactive label (Claim 34) or a reporter molecule (Claim 35); and pharmaceutical composition comprising the sequence of SEQ ID NO:16 and a carrier (Claim 36).

Claims 39-42 are interpreted as being drawn to a divalent scFV comprising amino acid sequence of SEQ ID NO:17 which binds to human CEA (Claim 39), further comprising a detectable agent (Claim 40), further where the detectable agent is a

radioactive label (Claim 41) or a reporter molecule (Claim 42); and pharmaceutical composition comprising the sequence of SEQ ID NO:16 and a carrier (Claim 43).

Claim 46 is interpreted as being drawn to a recombinant antibody comprising the sequence of SEQ ID NO: 16 or 17 which binds to human CEA.

The instant claimed monomeric scFv of SEQ ID NO:16 and the divalent scfv or diabody of SEQ ID NO:17 and pharmaceutical compositions comprising the same, were *prima facie* obvious at the time of the invention in view of Tormo, Freyre and Hollinger as evidenced by Ayala.

Tormo discloses the hybridoma CB/ior-CEA.1 which produces the murine Mab as being highly specific for human CEA with no cross-reaction with CEA-related molecules that shows no recognition of normal tissues, except for cells of the normal colon epithelium with polarized CEA expression. Applicants specification specifically teaches that the VH and VL domains comprising the scFv of SEQ ID NO:16 and 17 were derived from the antibody produced by the CB/ior-CEA.1 hybridoma of Tormo (see Example 1, p. 10, lines 35-39: "Total RNA from 10^6 cells of the mouse hybridoma CB/ior-CEA.1 (Tormo B. et al. APIMS. 97:1073-1080, 1989) was extracted with the TriPureTM reagent...") ("The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195

USPQ 430, 433 (CCPA 1997). Tormo does not disclose Ab constructs such a monomeric and diabody scFvs using the VH and VL domains from the parent antibody. Freyre as evidenced by Ayala and Hollinger rectifies this deficiency in its disclosure.

The scFv produced by Freyre et al. in 2000 using the VH and VL of CB/ior-CEA.1 was producible at high levels but reduced in affinity because numerous changes had been introduced into the VH/VL domains during PCR cloning as evidenced by Ayala. Ayala specifically teaches "A new scFv was constructed from newly amplified CB/ior-CEA.1 VH and VL genes, taking care to avoid the potential introduction of PCR mutations." And as evidenced by Ayala, Hollinger provided an alternative means for producing multivalent scFv forms and maintaining the integrity of the original VH and VL domain sequences of the parent antibody.

Hollinger discloses recombinant antibody fragments using variable domains encoded by genes from mouse hybridomas to make constructs for expressing scFv, bivalent and bispecific antibody fragments that have the advantages of retaining the antigen recognition of the parent antibody, being small in size, assembled in vivo and harvested directly from culture supernatant.

One skilled in the art would have been motivated to have combined the techniques of Tormo, Freyre and Hollinger as evidenced by Ayala to obtain an improved antibody fragment having the binding properties of the parent CB/ior-CEA.1 antibody and the advantages of being readily producible as a properly assembled and secreted antibody fragment by transfected cells in vitro or in vivo, and been reasonably assured of success in producing such based on the disclosures of Tomoro, Freyre as evidenced

by Ayala and Hollinger. The Tormo CEA antibody was highly selective and non-crossreactive for purposes of using such an antibody in targeted diagnostics or therapeutics for CEA-expressing tumors, and because obtaining smaller sized Ab fragments was more desirable for retaining antigen binding and for tumor penetration, one skilled in the art would have been motivated to have obtained scFv from the CB/ior-CEA.1 parent antibody based on Freyre, and because Freyre's scFv was already established at the time of the invention to retain antigen specificity albeit reduced affinity compared with the parent Ab as evidenced by Ayala, one would have been further motivated to have obtained an scFv or diabody which possessed reproducible and approximate binding properties to the parent Mab based on the disclosure of Hollinger for producing scFvs replicating the binding properties of the respective parent antibody. Taken together, one skilled in the art would have been reasonably assured of success in producing the instant claimed CEA antibody embodiments based on the disclosures of Tormo, Freyre as evidenced by Ayala and Hollinger because all the materials and reagents were available for producing the recombinant CEA Abs, and as evidenced by Freyre the importance of VH and VL sequence fidelity in generating a scFv with high affinity binding was established and Hollinger provided an alternative method to for cloning VH and VL domains from a parent Mab into a scFv or diabody structure in order to produce a smaller sized but high affinity antibody variant of the parental Mab. Further all of the reference appreciated obtaining small sized fragments for pharmaceutical applications.

Thus for the reasons above, the claims were *prima facie* obvious at the time of the invention over Tormo, Freyer as evidenced by Ayala and Hollinger.

Conclusion

24. No claims are allowed.
25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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